Predictive factors for early postoperative hypocalcemia after surgery for primary hyperparathyroidism

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The purpose of this study was to identify patients at risk for hypocalcemia after parathyroid surgery. The charts of 99 patients who underwent parathyroid surgery over a 2-year period using a rapid intraoperative parathyroid hormone (IOPTH) assay were retrospectively reviewed. Data for patient demographics, preoperative parathyroid hormone and calcium levels, IOPTH levels, and postoperative calcium levels were reviewed, and trends were analyzed for patients who had postoperative hypocalcemia. Of the 99 patients, 91 had one gland excised and 8 had two glands excised. Preoperative calcium levels ranged from 8.9 to 15.6 mg/dL. Sixty-seven of the patients had a >50% drop in IOPTH at 5 minutes, and 82 had a >50% drop in IOPTH by 10 minutes. Twelve patients had early hypocalcemia. Parathyroid weight and surgery type were not significant factors in predicting postoperative hypocalcemia. A drop of >80% in IOPTH at 10 minutes was a significant factor for postoperative hypocalcemia ($P = 0.02$). In addition, having normal or only minimally elevated preoperative calcium was an independent risk factor for postoperative hypocalcemia ($P = 0.05$). Our study has shown that postoperative calcium supplementation and in-hospital monitoring should be considered in patients with a preoperative calcium level in the normal range and with an IOPTH that has dropped by >80%.

Surgery remains the most effective treatment for hyperparathyroidism. The incidence of hyperparathyroidism is increasing secondary to increased detection, technological advances, awareness by providers, and routine serum calcium screening (1). While early guidelines suggested surgery in those with symptoms or significant hypercalcemia, more recent evidence suggests that earlier intervention in "asymptomatic" patients may prevent long-term complications such as bone disease, psychological morbidity, and possibly excess cardiovascular risk (2). The current move is away from traditional four-gland exploration into minimally invasive parathyroidectomy (2, 3). Proponents of minimally invasive parathyroidectomy feel that cure rates of over 95% comparable to four-gland exploration can be achieved with lower complication rates (2). Successful parathyroid surgery in this new paradigm relies on recent technological advances including focused ultrasound, ^{99m}technetium sestamibi scans, and the use of intraoperative parathyroid hormone (IOPTH). The combination of these technologies has proven better than using any one of them alone. For example, relying on sestamibi imaging alone can lead to failure, as 39% to 75% of multigland cases have solitary uptake on sestamibi imaging (3). The use of IOPTH in addition to good preoperative imaging can help reduce surgical failures.

The concept of IOPTH was first described by Nussbaum at Massachusetts General Hospital in 1988 (3). Parathyroid hormone (PTH) has a half-life as short as 1 to 3 minutes, which allows a drop in hormone levels to be measured on a clinically useful level during surgery (3, 4). The technique of using a two-site immunochemiluminometric assay to measure the active component of PTH (intact PTH) can provide IOPTH levels in as little as 15 minutes (3). Previous data analyzed from our institution have shown that in primary hyperparathyroidism, 90% of patients have appropriate assay decline by 5 minutes, and only 8% need the full 10 minutes to show adequate decline in PTH levels (5).

An important precept in parathyroid surgery is to avoid postoperative hypoparathyroidism and hypocalcemia. Symptomatic hypocalcemia is a significant postoperative morbidity for patients undergoing parathyroid surgery (6). Transient hypocalcemia occurs after surgery for primary hyperparathyroidism in 15% to 30% of patients (6–8). Hypocalcemia occurs in over 30% of patients in the reoperative setting (3, 9). Most hypocalcemia is transient, and permanent hypocalcemia is reported in only 0.5% to 3.8% of cases (7). Postoperative hypocalcemia is multifactorial (4). The blood supply to the parathyroid glands from the inferior thyroid artery is tenuous and sensitive to surgical manipulation (7). Other contributing factors include direct trauma to the parathyroid gland, inadvertent gland removal, hemodilution, "hungry bone syndrome," and thyrotoxic osteodystrophy (7). In addition, long-term hypercalcemic suppression of nonadenomatous parathyroid tissue makes remaining parathyroid tissue somewhat "stunned" when having to suddenly control calcium levels postoperatively (8). One sees a gradual recovery of the secretion of PTH by the

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remaining parathyroid glands that are no longer suppressed by the adenoma. It is during this period that a decrease in serum calcium is expected (10).

At our institution, a calcium level is typically drawn in the postanesthesia recovery unit within several hours after surgery; if patients are admitted to the hospital, it is drawn again in the morning. If these levels are normal, the patient is discharged. Practice varies among different surgeons as to how to supplement calcium in the hospital and after discharge. Symptomatic hypocalcemia is defined as symptoms such as paresthesias, Chvostek's sign, or Trousseau's sign. In severe hypocalcemia, life-threatening conditions such as tetany and cardiac dysrhythmias can develop (4). Patients who develop asymptomatic hypocalcemia are usually treated with oral calcium supplementation. Patients who develop symptomatic hypocalcemia are treated with intravenous calcium gluconate and/or oral vitamin D supplementation in addition to oral calcium (7).

Many surgeons are moving towards treating parathyroid and thyroid resections as outpatient procedures. Postoperative hypocalcemia after parathyroid surgery can take several days to manifest. Most studies have found that a significant drop in calcium is not evident until the third and fourth postoperative days (6). If patients are discharged prior to this point, they should be aware that hypocalcemia can develop even if the initial course was uneventful. So difficult is the current inability to identify patients at risk of clinically significant hypocalcemia that some experts advocate routine postoperative supplementation with calcium to facilitate early discharge (4). A readily available perioperative method to identify patients at risk of developing hypocalcemia would be beneficial (7).

This study analyzed data from our institution from patients with primary hyperparathyroidism in an attempt to identify factors predictive of early postoperative hypocalcemia. Preoperative and postoperative calcium levels, IOPTH assay results, and patterns of postoperative calcium supplementation were examined. We attempted to correlate preoperative or intraoperative factors that may predict postoperative hypocalcemia and the need for supplementation. We also attempted to identify which patients can be operated on safely with a day surgery–type procedure with or without calcium supplementation.

MATERIALS AND METHODS

We performed a retrospective chart review of a 2-year period from January 1, 2005, until December 31, 2006. All parathyroid surgeries for primary hyperparathyroidism were analyzed. Patients with resection of three or more glands for secondary or tertiary hyperparathyroidism were excluded. Data on preoperative calcium levels, IOPTH levels, and postoperative calcium levels were gathered. Blood samples were drawn during surgery at preincision, preexcision, 5 minutes after gland excision, and 10 minutes after gland excision. A drop in rapid IOPTH of 50% was considered adequate for primary hyperparathyroidism. We used the preincision value to calculate the percentage drop of IOPTH for the purpose of the study. The preexcision value is more prone to variation from manipulation of the neck during anesthesia and surgery and by early devascularization of the gland before the blood is drawn. Thus, the drop of rapid IOPTH was defined as follows:

$$\frac{(\text{Preincision PTH} - \text{Postexcision PTH})}{\text{Preincision PTH}} \times 100$$

Immediate postoperative calcium levels were those drawn postoperatively in the postanesthesia recovery unit, and postoperative day 1 levels were those drawn the morning after surgery on the wards. Any hypocalcemic values on either the immediate or postoperative calcium draws were considered as early postoperative hypocalcemia. Postoperative calcium supplementation patterns were also examined.

In patients who had early postoperative hypocalcemia, potential trends were analyzed for preoperative calcium levels, unilateral versus bilateral neck exploration, IOPTH levels and percentage drop, and postoperative supplementation. Data were summarized using descriptive statistics such as mean, standard deviation, and percentage. Chi-square analysis and logistic regression were utilized to evaluate the association between postoperative hypocalcemia and the variables of interest.

RESULTS

Ninety-nine patients (81 women and 18 men) had resections of adenomas for primary hyperparathyroidism during the study period. Preoperative calcium levels ranged from 8.9 to 15.6 mg/dL, and all patients had documented elevations of PTH prior to surgery, with a normal range of 10 to 74 pg/mL in our laboratory. Nineteen patients had bilateral explorations and 80 patients had unilateral explorations; 91 had one gland excised, and 8 had two glands excised for double adenomas (8% double adenoma rate). The weight of the excised parathyroid glands ranged from 100 to 4450 mg.

Sixty-seven of the patients had a >50% drop in IOPTH at 5 minutes, and 82 had a >50% drop in IOPTH at 10 minutes. Of the 17 patients whose IOPTH did not drop by 10 minutes, three had an adequate drop by 30 minutes postexcision. All eight of the patients who had excision of a double adenoma were among these 17 patients. In addition, three of the 17 had excision of the thyroid lobe containing the parathyroid gland, and three had identification and removal of a true single parathyroid adenoma.

Calcium levels were tested only in the postanesthesia recovery unit in 6 patients, only on postoperative day 1 in 28 patients, in both the postanesthesia recovery unit and on postoperative day 1 in 33 patients, and not at all in 32 patients who underwent outpatient-type procedures. The serum calcium levels ranged from 6.9 to 12.4 mg/dL in the immediate postoperative tests and from 6.9 to 11 on hospital day 1 (reference range, 8.4–10.2 in our laboratory); the ionized calcium levels ranged from 1.19 to 1.39 mmol/L in the immediate postoperative tests and from 1.04 to 1.39 on hospital day 1 (reference range, 1.13–1.32 in our laboratory).

Twelve patients had early hypocalcemia at one point during their perioperative hospitalization. No patients had documented symptomatic hypocalcemia, however. All of these patients had normal calcium levels off calcium supplementation at 3-month follow-up. The 10-minute drop in IOPTH, preoperative and

postoperative calcium values, patterns of supplementation, bilateral versus unilateral exploration, and parathyroid weights for these 12 patients are shown in *Table 1*.

Using a logistic regression model, several possible predictors of hypothyroidism were tested: preoperative calcium level, percentage drop of IOPTH at 5 and 10 minutes, unilateral versus bilateral exploration, and total parathyroid weight. Parathyroid weight and surgery type were not significant factors in predicting postoperative hypocalcemia. A drop of >80% in IOPTH at 10 minutes was a significant factor for postoperative hypocalcemia ($P = 0.02$). In addition, having normal or only minimally elevated preoperative calcium was an independent risk factor for postoperative hypocalcemia ($P = 0.05$) *(Table 2)*.

Table 1. Characteristics of 12 patients with postoperative hypocalcemia after surgery for primary hyperparathyroidism

Patient	10-min drop in IOPTH (%)	Calcium level (mg/dL)			Supplemental calcium at discharge	Exploration	Parathyroid weight (mg)
		Preoperative	Immediate postoperative	Postoperative day 1			
1	99	10.8	6.9	8.6	No	Unilateral	3060
2	93	10.1*	7.7	7.7	Calcium carbonate	Unilateral	558
3	83	1.56†	8.2	9.4	No	Bilateral	240
4	88	10.5	1.04†	NA	Os-Cal + D	Bilateral	237
5	87	11.0	NA	1.12†	No	Unilateral	1480
6	94	11.5	NA	6.9	Os-Cal + D	Bilateral	596, 361
7	89	11.1	9.6	7.8	No	Unilateral	3600
8	89	11.0	8.1	NA	No	Unilateral	209
9	82	11.2	8.2	NA	No	Bilateral	488
10	93	11.5	8.3	NA	No	Unilateral	600
11	88	8.9*	8.3	NA	No	Bilateral	Intrathyroid
12	86	10.8	8.3	NA	No	Unilateral	1560

*Normal level.

†Ionized calcium value (mmol/L).

IOPTH indicates intraoperative parathyroid hormone; NA, not available.

DISCUSSION

A critical understanding of the PTH assay's limitations and utility is necessary for its proper use. Past studies have found cure rates of 97% to 100% in patients with sporadic primary hyperparathyroidism using the IOPTH criteria of a >50% decline from baseline and a value within the normal range (3). Richards et al at the Mayo Clinic Rochester found that IOPTH monitoring had a sensitivity of 98% and specificity of 91% in primary operations, but the sensitivity dropped to 95% in patients with multiglandular disease (3). The reported incidence of multiglandular disease or multiple adenomas ranges from 6% to 28% in various reports, which is similar to a 6% incidence in our study (1, 3, 5).

Degradation of PTH begins within the parathyroid glands, and the fragments are then cleared by the liver and kidneys. Impairment of liver or renal function may prolong the breakdown of PTH and affect the IOPTH assay (3). Additionally, evidence exists that propofol can increase baseline PTH after a bolus. It is not known whether propofol increases PTH levels by stimulating secretion, delaying degradation, or interfering with the IOPTH assay (3). Multiple factors can affect the IOPTH assay, and a successful endocrine surgeon must factor these into decision making.

Postoperative hypocalcemia after surgery for primary hyperparathyroidism has an incidence ranging from 0% in some published studies up to 30% in others (11). Some groups give postoperative calcium supplementation to all patients. These groups typically have very few to no postoperative symptomatic hypocalcemic patients (12).

Table 2. Factors affecting postoperative hypocalcemia

Factor	*P* value
Parathyroid adenoma weight	0.44
Unilateral vs bilateral exploration	0.26
Normal to near-normal preoperative calcium levels	0.05*
>80% drop in IOPTH by 10 minutes	0.02*

*Significant.

IOPTH indicates intraoperative parathyroid hormone.

Surgeons have tried to define factors that could predict postoperative hypocalcemia and identify those patients who may need further monitoring or supplementation. Serum PTH levels can correlate to the weight of excised single parathyroid adenomas (13). No consensus has been reached, however, on whether parathyroid weight alone can predict postoperative hypocalcemia. A study by Westerdahl et al from Sweden found early hypocalcemia, defined as <4 days from surgery, in 26% of patients undergoing surgery for a single parathyroid adenoma. A bilateral neck exploration and a history of cardiovascular disease were independent risk factors for the development of early symptomatic hypocalcemia (6). The differences between the calcium levels in these patients became insignificant after 8 weeks, however. This same study also showed that preoperative normocalcemia is an independent predictor of late (>8 weeks later) postoperative hypocalcemia (6). In our study, a preoperative normocalcemia of <11 was associated with an increased risk

of early postoperative hypocalcemia but not with late hypocalcemia. A study from the Oregon Health Sciences University in Portland correlated the slope of two postoperative calcium values drawn within 24 hours of surgery. They found that a negative slope with a decrease in calcium from the first draw to the second correlated with an increased risk of having hypocalcemia in the following days (14). We did not graphically compare our postoperative calcium values, but this technique could be applied if one were to consistently draw at least two postoperative calcium values after surgery.

A study by Elaraj et al from the National Institutes of Health found that an IOPTH drop of 84% from baseline has a positive predictive value of 46% for identifying patients with single-gland disease undergoing reoperative parathyroid surgery who will require calcium and vitamin D supplements (9). In patients with multiple-gland disease, an 84% drop was associated with a 71% chance of requiring calcium and vitamin D supplementation (3, 9). These results are similar to our findings. We found that a >80% drop in IOPTH can be an independent predictor of early postoperative hypocalcemia.

Recent reports have analyzed whether parathyroid surgery can be done safely as an outpatient procedure. In one United Kingdom series of 50 patients operated on in a day-surgery setting, all were discharged with oral calcium of 800 mg twice daily and alfacalcidol 1 µg daily. No patient developed symptomatic hypocalcemia during the first 2 weeks after surgery, and after replacement was stopped, all patients had normal serum calcium levels at a mean follow-up of 26 weeks (2). Another United Kingdom series of 84 patients operated on for primary hyperparathyroidism had no documented cases of postoperative hypocalcemia (11). Of the patients in our study with postoperative hypocalcemia, all had normal serum calcium levels by the postoperative office visit several weeks later. This would imply that the majority of patients can be operated on safely in an outpatient setting and that long-term supplementation of calcium should not be necessary, as any postoperative hypocalcemia after surgery for primary hyperparathyroidism is largely transient.

CONCLUSIONS

Parathyroid surgery for primary hyperparathyroidism is occurring at earlier stages of the disease thanks to improved biochemical tests and awareness of the disease. Substantial cost benefit and patient care algorithms could be developed if factors that predict postoperative hypocalcemia could be identified. Clearly, patients with reoperative procedures or severe comorbidities should not be considered for outpatient-type procedures. Our study has shown that postoperative calcium supplementation and in-hospital monitoring should be considered in those patients with a preoperative calcium level in the normal range, below 11 in our laboratory, and with an IOPTH drop of >80%.

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